



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Barry, et al.
Serial No.: 09/841,413
Filed: April 24, 2001
For: Joint Repair Using Mesenchymal Stem Cells
Group: 3738
Examiner: Barrett

Commissioner for Patents
Box 1450
Alexandria, VA 22313-1450

BRIEF BEFORE THE BOARD OF APPEALS AND INTERFERENCES

SIR:

This is an appeal from the Final Rejection dated January 12, 2006.

REAL PARTY IN INTEREST

The real party in interest is Osiris Therapeutics, Inc., the assignee of the claimed subject matter of the above-identified application.

RELATED APPEALS AND INTERFERENCES

There are no related appeals and interferences with respect to the above-identified application.

STATUS OF CLAIMS

Claims 1-27 have been canceled without prejudice.

Claims 28-77 are pending, stand finally rejected, and are before the Board on appeal. These claims are listed in the Appendix attached hereto.

STATUS OF AMENDMENTS

No amendments after the Final Rejection have been filed.

SUMMARY OF CLAIMED SUBJECT MATTER

The present invention is directed to regenerating meniscal tissue in a joint (as defined broadly in Claim 28) and to repairing meniscal damage in a joint (as defined broadly in Claim 35) and thereby to reducing or preventing changes in the joint resulting from meniscal damage, including reducing subchondral bone sclerosis in a joint (as defined broadly in Claim 42), preventing or reducing the formation of osteophytes in a joint (as defined broadly in Claim 49), and protecting cartilage in a joint of an animal (as defined broadly in Claim 56), by injecting into the joint a liquid suspension consisting essentially of mesenchymal stem cells and an acceptable pharmaceutical carrier. The mesenchymal stem cells differentiate into and/or stimulate production of meniscal tissue. The mesenchymal stem cells are injected in an amount effective to regenerate meniscal tissue in a joint, to repair meniscal damage in a joint, to reduce subchondral bone sclerosis in a joint, to prevent or reduce the formation of osteophytes in a joint, or to protect cartilage in a joint of an animal.

Support for Claims 28 and 35 is found in the specification in the first and second paragraphs of Page 5, the second paragraph of Page 6, and in Examples 1 through 4, at Pages 8 through 27.

Support for Claim 42 is found in the specification in the second paragraph of Page 1, the first and second paragraphs of Page 5, the second paragraph of Page 6, and in Examples 1 through 4, at Pages 8 through 27.

Support for Claim 49 is found in the specification in the second paragraph of Page 1, the first and second paragraphs of Page 5, the second paragraph of page 6, and in Examples 1 through 4, at Pages 8 through 27, and in particular in Example 2 at the second paragraph of Page 17, and in Example 3 at the paragraph bridging Pages 23 and 24.

Support for Claim 56 is found in the specification in the first and second paragraphs of Page 5, the second paragraph of Page 6, and in Examples 1 through 4, at Pages 8 through 27, and in particular in Example 2 at the paragraph bridging Pages 17 and 18.

GROUND OF REJECTION TO BE REVIEWED ON APPEAL

The following grounds of rejection are to be reviewed on appeal:

The rejection of Claims 28-30, 34-37, 41-44, 48-51, 55-58, 62, and 63-77 under 35 U.S.C. 102(e) as being anticipated by Abatangelo, et al.

The rejection of Claims 28, 31-33, 35, 38-40, 42, 45-47, 49, 52-54, 56, and 59-61 under 35 U.S.C. 102(b) as being anticipated by Goldberg, et al.

ARGUMENT

A. The Rejection of Claims 28-30, 34-37, 41-44, 48-51, 55-58, 62 and 63-77 Under 35 U.S.C. 102(e) as Being Anticipated by Abatangelo, et al.

The claimed invention, in essence, is directed to injecting into a joint a liquid suspension consisting essentially of mesenchymal stem cells and an acceptable pharmaceutical carrier. The mesenchymal stem cells are administered in an amount effective to generate meniscal tissue.

The Federal Circuit has held that anticipation is established only if all elements of an invention, as stated in a patent claim, are identically set forth in a single prior art reference. All of the limitations must be disclosed by the reference either expressly or inherently. (See *Mehl/Biophile International Corp. v. Milgraum*, 192 F.3d 1362 (Fed.Cir. 1999) at 1365; 52 U.S.P.Q.2d 1303, at 1306; *Oney v. Ratliff*, 182 F.3d 893 (Fed. Cir. 1999); 51 U.S.P.Q.2d 1697; *Finnigan Corp. v. U.S. International Trade Commission*, 180 F.3d 1354 (Fed. Cir. 1999), at 1367; 51 U.S.P.Q.2d 1001, at 1009; *General Electric Co. v. Nintendo Co., Ltd.*, 179 F.3d 1350 (Fed. Cir. 1999), at 1356, 50 U.S.P.Q.2d 1910, at 1915.)

Applicants assert that Abatangelo does not disclose all elements of Applicants' claimed invention and therefore does not anticipate the claimed invention. Abatangelo does not disclose the injection of a liquid suspension of mesenchymal stem cells into a joint in an effective amount in order to generate meniscal tissue.

Abatangelo is nothing more than a generic disclosure directed to a composition which includes mesenchymal stem cells in a carrier which is a hyaluronic acid derivative. The mesenchymal stem cells and the hyaluronic acid derivative may be administered to an animal, whereby the mesenchymal stem cells may differentiate into various types of tissues. The case law is clear, however, that a reference which discloses a genus does not disclose inherently all species within such genus. (See Metabolite Laboratories v. Laboratory Corp. of America, 71U.S.P.Q. 2d1081 (C.A.F.C. 2004), at 1091; Corning Glass Works v. Sumitomo Electric U.S.A., Inc., 9U.S.P.Q. 2d1962 (C.A.F.C.1989), at 1970.)

The issue before the Board is whether Abatangelo's generic disclosure of mesenchymal stem cells in a hyaluronic acid-based carrier, wherein the mesenchymal stem cells and the carrier are administered to an animal in order to generate any of a variety of tissues in the animal, is sufficient to anticipate Applicants' claimed invention of injecting a liquid suspension of mesenchymal stem cells into a joint in an effective amount in order to generate meniscal tissue. Abatangelo discloses, at Column 7, lines 17-23, that the mesenchymal stem cells in the hyaluronic acid-based carrier can differentiate into any of a wide variety of cell lineages, including osteogenic, chondrogenic, tendonogenic, ligamentogenic, myogenic, marrow stromagenic, adipogenic, and dermagenic, which form bone, cartilage, tendons, ligaments, muscles, fat, and skin. Therefore, there are a multitude of tissues which may be generated from the products of Abatangelo which include mesenchymal stem cells in a hyaluronic acid-based carrier. In addition, Abatangelo also discloses at Column 8, lines 20-29, that the carrier may be any of a wide variety of forms, such as a sponge, fabric, gel, slurry, powder, or injectable fluid.

Thus, there are many possible combinations of the form of carrier and the type of tissue into which the mesenchymal stem cells may differentiate. In light of the multitude of combinations, and when taken in its entirety, Abatangelo does not describe or even remotely suggest to one of ordinary skill in the art the injection of a liquid suspension of mesenchymal stem cells into a joint in an effective amount in order to generate meniscal tissue. (See Ultradent Products Inc. v. Life-Like Cosmetics Inc., 44 U.S.P.Q. 2d 1336 (C.A.F.C.1997), at 1342; Bristol-Myers Squibb Co. v. Ben Venue Laboratories Inc., 58 U.S.P.Q. 2d 1508 (C.A.F.C.2001), at 1517.)

Abatangelo is a reference only for which it teaches. Corning Glass Works, *supra*, at 1970.

It is clear that from reading Abatangelo that Abatangelo does not teach the claimed invention. Abatangelo describes and teaches mesenchymal stem cells contained in a three-dimensional matrix. Although Abatangelo makes a passing reference that the matrix may be an injectable fluid, it is clear that the preferred embodiments of the matrix are solids, such as in the form of a sponge (column 8, lines 20-21, Examples 1, 2, 4), or a fabric (Examples 3, 4, 5, 9, 10, and 11), or a solid implant onto which mesenchymal stem cells are seeded (Examples 6 and 7). None of the examples in Abatangelo employ a liquid suspension of mesenchymal stem cells.

Example 7 discloses the use of the cell matrix and mesenchymal stem cells in a meniscus repair study. Example 7 states that composites were prepared as described in Example 6. Example 6 describes the composites as suspensions of mesenchymal stem cells that were loaded onto solid hyaluronic acid based carriers. Example 7 states that the composites were sutured to the lateral meniscus, the coronal meniscus, the synovial lining, and the posterior half of the meniscus. Thus, Example 7 teaches the repair of meniscus with an implant including bone marrow derived cells that were absorbed or loaded onto a solid hyaluronic acid based carrier, and the implant was sutured to a damaged meniscus.

The Court of Appeals for the Federal Circuit and its predecessor, the Court of Customs of Patent Appeals, have found that there was no anticipation in similar situations.

For example, in Ultradent Products, supra, the defendant in a patent infringement suit challenged the validity of a patent claim it was accused of infringing, based on a prior art reference. The defendant had alleged that the reference anticipated the patent claim. The patent claim in issue was directed to a dental bleaching composition having a matrix material with a sufficiently high viscosity to provide for the bleaching agent to be in contact with the tooth surfaces for greater than about 2 hours and a stickiness sufficient to retain a dental tray in place

over the teeth for a period of time greater than about 2 hours. The reference disclosed a bleaching composition including carboxypolymethylene in an amount of from 0.05% to 5% Id., at 1341-1342. Testing conducted during litigation over the validity of the patent claim showed that compositions containing 3% and 5% carboxypolymethylene provided the level of viscosity and stickiness required by the claim. Id., at 1341.

The Federal Circuit held that, in order for the claim to be invalid, one had to show that the reference described to one of skill in the art "the tested combinations, or other combinations meeting the limitations of the claims, from among the many possible candidates." Id., at 1342.

Abatangelo discloses a multitude of possible combinations of forms of carrier for mesenchymal stem cells and the types of tissue into which the mesenchymal stem cells may differentiate. There is no description or teaching in Abatangelo, for one skilled in the art, from the multitude of combinations described therein, to put an effective amount of mesenchymal stem cells into an injectable liquid suspension, and inject such liquid suspension of an effective amount of mesenchymal stem cells into a joint in order to repair meniscal tissue. Therefore, Abatangelo does not anticipate the claimed invention.

In In Re Arkley, 172 U.S.P.Q. 524 (C.C.P.A. 1972), the claim in issue was directed to a specific cephalosporin-type antibiotic having a specific formula and structure. The Board of Appeals had upheld the rejection of such claim under 35 U.S.C.102(e) as being anticipated by a reference, a patent issued to Flynn, disclosing cephalosporin compounds having a certain generic formula that encompassed the claimed compound. Id., at 525. The Court of Customs and Patent Appeals reversed the decision of the Board of Appeals because "there is nothing in the teachings relied upon by the Patent Office which clearly and unequivocally directs those skilled in the art

to make this selection nor any indication that Flynn [i.e., the inventor of the cited reference] ever made the selection himself." Id., 526.

Although Column 8, lines 20-37 of Abatangelo state that the matrix may be in any of a variety of forms, there is nothing in Abatangelo which directs those skilled in the art "clearly and unequivocally" to select and administer an injectable suspension of mesenchymal stem cells in a hyaluronan based carrier when repairing meniscal tissue, and, similar to the situation in Arkley, there is no indication in Abatangelo that Abatangelo ever selected an injectable suspension of mesenchymal stem cells in a hyaluronan based carrier when repairing meniscal tissue. In fact, when Abatangelo undertook an experiment to repair damaged meniscal tissue, Abatangelo elected to use a solid hyaluronic acid based implant containing bone marrow derived cells. Thus, Abatangelo provides no direction to one skilled in the art to select a liquid hyaluronan based carrier for mesenchymal stem cells when employing such mesenchymal stem cells in repairing damaged meniscal tissue. Furthermore, Applicants' claims require that the liquid suspension contain an effective amount of mesenchymal stem cells. Because Abatangelo does not direct one skilled in the art to select an injectable suspension of mesenchymal stem cells to repair damaged meniscal tissue, Abatangelo also does not direct one skilled in the art to inject a suspension of an effective amount of mesenchymal stem cells to repair damaged meniscal tissue. Therefore, Abatangelo does not anticipate Applicants' claimed invention under 35 U.S.C. 102 (e).

Furthermore, in Example 7, at Column 14, lines 52-54, it is stated that "The knee joint was carefully dissected and the meniscus harvested and processed for histological analysis." There are, however, no results provided by Abatangelo of such analysis. Thus, Abatangelo provides no evidence that the implantation of the esterified hyaluronic acid carrier containing mesenchymal stem cells resulted in meniscal repair. Even if there were results that did show that

the implant of Abatangelo was implanted successfully, the only teaching contained in Abatangelo regarding the regeneration and/or repair of meniscal tissue is to employ a solid implant containing mesenchymal stem cells.

In sum, Abatangelo provides a broad generic disclosure of mesenchymal stem cells in a hyaluronic acid-based carrier, and the administration of the mesenchymal stem cells in such carrier in order to effect the differentiation of such mesenchymal stem cells into any of a variety of tissues. Such generic disclosure encompasses a multitude of species; however, many of such species are not taught by Abatangelo, and at best, Abatangelo provides merely an invitation to investigate or experiment. Metabolite Laboratories, supra, at 1091. It is clear from reading Abatangelo that Abatangelo does not teach the injection of a liquid suspension of mesenchymal stem cells into a joint in an effective amount in order to generate meniscal tissue. At best, Abatangelo's disclosure is an invitation to investigate or an invitation to further experimentation with respect to administering a liquid suspension of mesenchymal stem cells in order to generate meniscal tissue. Furthermore, although Abatangelo provides an example, i.e., Example 7, for repairing meniscal tissue, such example only discloses using bone marrow derived cells in solid hyaluronic acid-based carriers. Such example shows that, with respect to meniscal repair, Abatangelo contemplated only the use of a solid carrier. Such a disclosure clearly does not meet the standard for anticipation under 35 U.S.C.102.

As further evidence that the art, at the time of Applicants' invention of the claimed subject matter did not disclose or even remotely suggest to one of ordinary skill in the art the injection of a liquid suspension of mesenchymal stem cells in an amount effective to repair or regenerate meniscal tissue, Applicants submitted with an Information Disclosure Statement on January 14, 2003, a paper by Walsh, et al., Tissue Engineering, Vol. 5, No. 4, pgs. 327-337

(1999). In Walsh, a partial anterior medial meniscectomy was performed in rabbits by resection the meniscus just anterior to the medial collateral ligament. The rabbits were treated with a Type I collagen sponge loaded with mesenchymal stem cells. Walsh described the results of the experiment at Page 336, lines 1-5 and 11-16. At Page 336, lines 1-5, Walsh noted, with respect to the collagen sponge implant which included the mesenchymal stem cells, that:

As with the sponge alone, in this group there was failure of the anterior attachment, likely due to the lack of tensile strength of the collagen sponge It is likely that the inflammatory response caused by the collagen sponge precludes its further use in the joint environment.

At page 336, lines 11-16, Walsh noted further:

“The addition of bone marrow derived mesenchymal stem cells to the collagen sponge enhanced fibrocartilage regeneration in this model. However, the current scaffold lacks initial tensile strength that will provide load-bearing function at the time of implantation. Because the meniscus functions in load bearing by the generation of circumferential tensile stress, the anterior and posterior attachments are of critical importance. These must be secure before significant weight bearing occurs in the regenerated meniscus; otherwise failure is certain.”

Walsh emphasizes the importance of using a solid implant which includes mesenchymal stem cells for regenerating or repairing meniscal tissue. Although the collagen sponge loaded with mesenchymal stem cells as described in Walsh failed, such failure was not because the collagen was a solid, but because the collagen sponge lacked sufficient tensile strength to become anchored within the joint, and because the collagen sponge elicited an inflammatory response. Walsh emphasizes that in order to regenerate or repair meniscal tissue, one needs to provide mesenchymal stem cells in a solid implant which will be of sufficient tensile strength to become anchored in the joint, and which will not elicit an inflammatory response.

Therefore, Walsh is further evidence that, if one wished to repair or regenerate meniscal tissue, with mesenchymal stem cells, one would select a solid carrier for such mesenchymal stem

cells, not an injectable liquid suspension. Thus, one skilled in the art, when considering the state of the art at the time of Applicants' invention with respect to using mesenchymal stem cells for repairing or regenerating meniscal tissue, as taught by Abatangelo and Walsh, would have selected a solid carrier for such mesenchymal stem cells. Although Abatangelo discloses an injectable fluid as a carrier for mesenchymal stem cells, Abatangelo does not teach one skilled in the art to select an injectable fluid as a carrier for mesenchymal stem cells when using mesenchymal stem cells to repair or regenerate meniscal tissue.

Therefore, Abatangelo does not anticipate Applicants' invention as claimed, and it is therefore respectfully requested that the rejection under 35 U.S.C.102(e) be reversed.

B. The Rejection of Claims 28, 31-33, 35, 38-40, 42, 45-47, 49, 52-54, 56, and 59-61 Under 35 U.S.C. 102(b) as Being Anticipated by Goldberg, et al.

As noted hereinabove, Applicants' claims are directed to injecting into a joint a liquid suspension of mesenchymal stem cells in an effective amount to generate meniscal tissue.

Goldberg discloses the administration of mesenchymal stem cells to regenerate damaged articular cartilage as a result of osteoarthritis. The mesenchymal stem cells may be contained in a gel suspension, such as a collagen gel, a fibrin glue, or an autologous fibrin gel, or in a liquid suspension in autologous serum or buffered saline, or in a moldable gel such as a thick collagen gel suspension.

As will be explained in further detail below, articular cartilage is not meniscal tissue. Goldberg, which is directed solely to the administration of mesenchymal stem cells in order to repair articular cartilage, provides no guidance with respect to injecting a liquid suspension of mesenchymal stem cells into a joint in an effective amount in order to generate meniscal tissue. All Goldberg teaches to one skilled in the art is to administer mesenchymal stem cells in a gel

suspension, a liquid suspension, or a moldable gel in order to repair articular cartilage. Because articular cartilage is not meniscal tissue, one skilled in the art would not look to Goldberg and the teachings contained therein for guidance when one desired to administer mesenchymal stem cells in an effective amount to generate meniscal tissue.

Goldberg, at Pages 29 and 30, describes a rabbit model of osteoarthritis in which about 30% of the anterior aspect of the medial meniscus was removed. Although Goldberg describes the removal of a portion of the meniscus, Goldberg's description does not state that Goldberg injected into a joint a liquid suspension of mesenchymal stem cells in an effective amount in order to generate meniscal tissue. All that Goldberg's description of the rabbit model of osteoarthritis discloses is the extent of cartilage damage after the meniscectomy, and that repair of focal full-thickness defects of articular cartilage (which is not meniscal tissue) and subchondral bone appears to depend on the age of the animal and size of the defect. There is no mention of the repair of damaged meniscal tissue.

At Page 30, Goldberg also describes a dog model for repair of articular cartilage of the knee. In the dog model, the anterior cruciate ligament is transected by lateral arthrotomy, and gel implants of mesenchymal stem cells are made arthroscopically into one or more lesion sites on the articular surface. The dog model, like the rabbit model, does not describe the injection of a liquid suspension of mesenchymal stem cells into a joint in an effective amount in order to repair or regenerate meniscal tissue.

Example 3 describes a rabbit model for regenerating articular cartilage destroyed by osteoarthritis. In such model, full-thickness defects were made on the weight bearing surface of the medial femoral condyle. Mesenchymal stem cells in a Type I collagen gel then were implanted into the defects. In such animal model, the mesenchymal stem cells were not

administered to meniscal tissue, and the mesenchymal stem cells were contained in a collagen gel and implanted. They were not in a liquid suspension and injected.

It is clear, therefore, from reading Goldberg, that none of the animal models described or used by Goldberg, which are directed to repairing articular cartilage, were directed to the injection of a liquid suspension of mesenchymal stem cells into a joint in an effective amount in order to generate meniscal tissue.

Instead of repairing meniscal tissue, Goldberg is directed to the administration of mesenchymal stem cells in the treatment of osteoarthritis. Goldberg discloses the use of animal models to induce osteoarthritis, followed by the administration of mesenchymal stem cells in order to repair articular cartilage damage resulting from osteoarthritis.

Goldberg desires to repair articular cartilage damage caused by osteoarthritis by administering mesenchymal stem cells. There is no disclosure or suggestion in Goldberg to repair meniscal tissue as claimed by Applicants, and no disclosure or suggestion in Goldberg as to administering a liquid suspension of mesenchymal stem cells in an effective amount in order to repair meniscal tissue.

The Examiner is taking the position that, if one follows the teachings of Goldberg, that one inherently will repair meniscal tissue and thus Goldberg anticipates the claimed invention.

In making such a rejection, however, the Examiner has overlooked that:

“Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient”. (In Re Robertson, 169 F.3d 743 (Fed. Cir. 1999), at 745, 49 U.S.P.Q. 2d 1949, at 1950-1951, citing Continental Can Co. v. Monsanto Co., 948 F.2d 1264 (Fed. Cir. 1991), at 1269, 20 U.S.P.Q. 2d 1746, at 1749, and In Re Oelrich, 666 F.2d 578 (Ct. Cust. Pat. App. 1981), at 581, 212 U.S.P.Q. 323, at 326). (emphasis added).

As will be explained in further detail hereinbelow, all that Goldberg discloses is that mesenchymal stem cells may be used to regenerate damaged articular cartilage as a result of osteoarthritis. The claims on appeal require that the mesenchymal stem cells be administered in an amount effective to repair meniscal tissue. There is nothing in Goldberg which would lead one skilled in the art to believe that by following the teachings of Goldberg, one also can repair meniscal tissue in that Goldberg does not teach the administration of mesenchymal stem cells in an amount effective to repair meniscal tissue. Assuming solely for the sake of argument that, by following the teachings of Goldberg, one may repair damaged meniscal tissue, such a result is only a mere possibility in that Goldberg is directed to the regeneration of articular cartilage, and there is nothing in Goldberg which states that using an injectable suspension of mesenchymal stem cells to regenerate articular cartilage defects includes such mesenchymal stem cells in an amount effective to repair meniscal tissue. Applicants' claims state that the mesenchymal stem cells are injected into a joint in an effective amount to repair or generate meniscal tissue. Because Goldberg is directed solely to the repair of articular cartilage, Goldberg provides no guidance to one skilled in the art as to the injection of a liquid suspension containing an effective amount of mesenchymal stem cells to repair or generate meniscal tissue. Therefore, there is no basis in Goldberg for asserting that following the teachings of Goldberg also result inherently in the repair of meniscal tissue which, as stated hereinbelow, has properties different from that of articular cartilage.

Furthermore, Applicants assert that:

"To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence."

(Continental Can, supra, 948 F.2d 1264, at 1268, 20 U.S.P.Q. 2d 1746, at 1749).

Goldberg is silent with respect to whether, if one uses an injectable suspension of mesenchymal stem cells disclosed to repair articular cartilage defects, such mesenchymal stem cells are administered in an amount effective to repair meniscal tissue. Because Goldberg is silent with respect to whether, in regenerating articular cartilage, one also has administered the mesenchymal stem cells in an amount effective to repair meniscal tissue, it is incumbent upon the Examiner to present extrinsic evidence which shows that the articular cartilage repair treatments disclosed by Goldberg also necessarily will result in the repair of meniscal tissue. The Examiner has failed to provide any such extrinsic evidence. Therefore, any assertion by the Examiner that meniscal tissue repair inherently will result by following the teachings of Goldberg is based on mere possibilities, and sheer speculation, and is insufficient to support the anticipation rejection based upon Goldberg.

By repairing meniscal tissue, Applicants prevent osteoarthritis from occurring. In contrast, Goldberg discloses the administration of mesenchymal stem cells after osteoarthritis has developed, and there is nothing in Goldberg that even remotely suggests to one of ordinary skill in the art that such administration of mesenchymal stem cells after the onset of osteoarthritis results in the repair of meniscal tissue. Goldberg is directed solely to the treatment of osteoarthritis and the repair of articular cartilage damaged as a result of osteoarthritis. Nothing in Goldberg's disclosure would lead one of ordinary skill in the art to expect reasonably that mesenchymal stem cells were administered to a joint in an effective amount in order to repair meniscal tissue.

Furthermore, Goldberg's sole objective of regenerating articular cartilage that has been damaged as a result of osteoarthritis is mentioned throughout the Goldberg application, as exemplified by the following passages:

“Once the condition [i.e., osteoarthritis] has progressed to substantial articular cartilage damage, none of the currently available approaches are adequate.”

(Page 3, lines 17-19)

“The most promising approach to articular cartilage repair appears to be the use of autologous mesenchymal stem cells, which are osteochondral precursors.”

(Page 5, lines 18-20)

“A characteristic indicator of chondral defect is a visibly altered gait or use of the joint to accommodate the discomfort or stiffness resulting from tissue damage, and the objective of treatment is to regenerate full thickness articular cartilage at the site of the defects to thereby prevent the joint destabilization and rapid joint destruction which are common sequelae of advanced osteoarthritis.”

“Patients ranging in age from 30-50 years with one or more well-defined articular cartilage lesions (as determined by imaging modalities or diagnostic arthroscopy) are ideal candidates for treatment in accordance with the invention.”

(Page 6, lines 15-27)

“The implants of the invention are indicated for use in regenerating articular cartilage which has been lost through degenerative osteoarthritis.”

(Page 11, lines 4-6)

“Implants containing autologous human mesenchymal stem cells are chondrogenic and, as such, regenerate hyaline cartilage directly at the graft site where they are able to differentiate into cartilage-forming chondrocytes.”

(Page 11, lines 10-13)

Regulation of Chondrogenesis

“This aspect focuses on the identification of molecules regulating mesenchymal stem cells during chondrogenic differentiation, including factors controlling the development of articular hyaline cartilage. To regenerate hyaline cartilage in osteoarthritis patients

under a variety of clinical scenarios, it is important to develop a better understanding of the molecules that control the chondrogenic lineage progression of human mesenchymal stem cells.”

(Page 17, line 28 – Page 18, line 3)

“.... 2) once committed, the mesenchymal stem cell-derived progeny cells are capable of progressing toward articular chondrocytes.”

(Page 18, lines 13-15)

“The implant, device and/or composition of the invention utilizes autologous mesenchymal stem cells in a gel, liquid, or molded configuration to regenerate the articular, hyaline cartilage via the developmental course seen during embryonic differentiation.”

(Page 30, line 33 – Page 31, line 2)

“The mesenchymal stem cells in the liquid suspension home directly towards the sites of lesions on the articular surface.”

(Page 31, lines 30-32)

“The ultimate goal of the product development program is to regenerate articular cartilage destroyed by osteoarthritis.”

(Page 34, lines 12-14)

Applicants' claimed invention, in contrast, is directed to the repair and regeneration of meniscal tissue. Meniscal tissue is not articular cartilage. Articular cartilage is hyaline cartilage, while meniscal tissue is fibrocartilage, as indicated in Buckwalter, et al., Orthopaedic Basic Science, 2nd Edition, American Academy of Orthopaedic Surgeons, Chapter 17, page 444, column 2, lines 17 and 18, page 445, column 2, line 15 and page 446, column 1, line 6, Table 1, page 445, Figure 3, page 446, and Chapter 20, page 532, column 1, lines 2 and 3. A copy of Chapters 17 and 20 of Buckwalter was submitted previously.

The Examiner bases his rejection upon two passages in Goldberg i.e., Page 4, line 33 to Page 5, line 9 and Page 6, lines 1-9.

Page 4, line 33 to Page 5, line 9 reads as follows:

For repair of cartilage damaged as part of the degenerative effects of osteoarthritis; the present inventors have found that the human mesenchymal stem cell approach makes it possible to: (1) regenerate both shallow cartilage chondral defects and full thickness cartilage defects (osteochondral lesions); (2) broaden the suitable clinical population to routinely include middle-aged patients; (3) eliminate the use of autologous tissue grafts (mature cartilage and the periosteal covering) to repair an articular cartilage injury; (4) regenerate other types of cartilage such as patellar and spinal disk cartilage; (5) regenerate articular joint cartilage in older patients with osteoarthritis; and (6) form new cartilage and subchondral bone which fully integrate into the adjacent normal tissue.

None of the above-mentioned applications, however, is directed to the repair of meniscal tissue.

Page 6, lines 1-9 read as follows:

Several formulations of autologous, culture-expanded mesenchymal stem cells that serve as the basis of therapies for osteoarthritis are contemplated depending on the stage, joint location and severity of the disease. They are (1) a gel formulation that can be applied to osteochondral defects during arthroscopy; (2) an injectable cell suspension for delivery directly to the synovial space; and (3) a molded mesenchymal stem cell-biomatrix product to re-surface joint surfaces in advanced cases.

This passage, when read in context with the two paragraphs following such passage, such two paragraphs including Page 6, lines 15-27 cited hereinabove, indicates clearly to one skilled in the art that the injectable cell suspension would be used to repair articular cartilage defects, as opposed to meniscal tissue as claimed by Applicants, and thus would provide no guidance to one

skilled in the art to inject a liquid suspension of mesenchymal stem cells in an amount effective to repair meniscal tissue.

Therefore, the two above-mentioned passages of Goldberg provide no basis for a rejection under 35 U.S.C 102(b).

In addition, as stated previously in Applicants' Amendment filed January 14, 2003, meniscus and articular cartilage have different compositions, structures, and mechanical functions. The major macromolecule in the meniscus is Type I collagen, which has two $\alpha 1$ chains and one $\alpha 2$ chain. (See Adams, et al., Knee Meniscus: Basic and Clinical Foundations, Chapter 2, pages 15-28, Raven Press, Ltd., New York, (1992), a copy of which was submitted with Applicants' Amendment filed January 14, 2003), while the major component of articular cartilage is Type II collagen, which has three $\alpha 1$ chains. (See also, Naumann, et al., J. Histochem. and Cytochem., Vol. 50, No. 8, pages 1049-1058 (2002), at Table 2, page 1053. A copy of Naumann accompanied the Amendment of January 14, 2003.) In addition, although some Type X collagen is found in articular cartilage, no Type X collagen has been found in meniscus. Furthermore, meniscus contains significantly less glycosaminoglycans (GAG) than hyaline cartilage. (See Naumann, at page 1053, column 2, lines 17-20 and 32-35, and Table 2.) The collagen content of articular cartilage is about 60% of the dry tissue weight (Mankin, et al., Osteoarthritis, Diagnosis and Medical/Surgical Management, Chapter 5, Moskowitz, et al., Eds., Philadelphia, W.B. Saunders Company (1992), pages 109-154, at page 111, a copy of which was submitted with Applicants' Amendment filed January 14, 2003), while meniscus has a collagen content up to 75% of its dry tissue weight. (See Adams, et al., page 17, column 2, line 27.) The proteoglycan content of the meniscus has been reported to be from about one-twentieth to about

one-eighth of that in articular cartilage. (See Buckwalter, et al., at page 534, column 1, lines 25-27 and Adams, et al., page 22, column 2, lines 9-11.)

In addition, articular cartilage is divided into superficial, intermediate, and deep zones; and the collagen fiber orientations and proteoglycan contents vary in each zone. In the meniscus, the collagen fibers predominantly are in a circumferential arrangement, and they act as reinforcement for the meniscus to resist tensile stresses. (See Adams, et al., pages 19 and 20 and Buckwalter, et al., page 533, column 2, line 35 to page 534, column 1, line 1.)

Also, the stiffness of the meniscus along the collagen fibers (i.e., in the circumferential direction) is one to two orders of magnitude higher than that of articular cartilage. (See Setton, et al., Clinical Orthopaedics and Related Research, number 367S, pgs. S254-S272, Lippincott, Williams & Wilkins, 1999, a copy of which was submitted with Applicants' Amendment filed January 14, 2003). This high stiffness along the collagen fibers enables the meniscus to resist large circumferential stresses that arise when it is loaded. The resistance to fluid flow (which is proportional to the inverse of the hydraulic permeability) of the meniscus is about 6 to 10 times that of articular cartilage, so that the meniscus resists fluid exudation to a greater extent than cartilage. (See Setton, et al., pg. S258, column 2 and pg. S259, column 1, and Buckwalter, et al., pg. 535, column 2, lines 6-9). The lower permeability of the meniscus allows the meniscus to remain pressurized for longer time periods after loading, so the meniscus acts as a fluid-filled cushion. In addition, meniscus has approximately half the elastic modulus of articular cartilage. (See Buckwalter, et al., page 535, column 2, lines 6-9.) Because meniscus and articular cartilage have different compositions, structures, and mechanical functions, Goldberg, which discloses the use of mesenchymal stem cells to regenerate damaged articular cartilage as a result of osteoarthritis, provides no basis for one skilled in the art to believe that the mesenchymal stem

cells administered to effect the regeneration of articular cartilage also were administered in an amount effective to repair meniscal tissue, and therefore Goldberg provides no basis for one skilled in the art to inject into a joint a liquid suspension of mesenchymal stem cells in an amount effective to repair meniscal tissue.

Furthermore, Applicants' claims are directed to the injection into a joint of a liquid suspension of mesenchymal stem cells in order to regenerate or repair meniscal tissue. Although Goldberg discloses that a liquid suspension of mesenchymal stem cells may be introduced directly into the synovial cavity, Goldberg does not state that the introduction of such liquid suspension will repair or regenerate meniscal tissue. More particularly, the last paragraph of Page 31 of Goldberg states as follows:

The second formulation is a liquid suspension of autologous mesenchymal stem cells either in autologous serum or buffered saline that can be introduced directly into the synovial cavity. The mesenchymal stem cells in the liquid suspension home directly towards the sites of lesions on the articular surface. High doses ($>10^8$ cells) of mesenchymal stem cells can be infused without clumping and without ectopic tissue formation. (emphasis added).

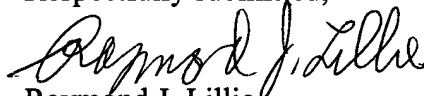
Thus, Goldberg teaches that if one administers a liquid suspension of mesenchymal stem cells to the synovial space, the mesenchymal stem cells will home directly to the articular surface to repair lesions on the articular surface, i.e., to repair articular cartilage. Thus according to Goldberg, the administration of a liquid suspension of mesenchymal stem cells to the synovial space will not result in the repair or regeneration of meniscal tissue. Therefore, one skilled in the art, when reading Goldberg, would not expect that the administration of a liquid suspension of mesenchymal stem cells to the synovial space would result in the repair and regeneration of meniscal tissue. Instead, Goldberg leads one to believe that a tissue having a different composition, function, and structure than meniscal tissue would be repaired. Because Goldberg

leads one skilled in the art to believe that the administration of mesenchymal stem cells to a joint would result in the repair of articular cartilage, which has a different composition, function, and structure than meniscal tissue, one skilled in the art is provided with no guidance from Goldberg with respect to administering a liquid suspension of mesenchymal stem cells in an effective amount to repair or regenerate meniscal tissue.

Because Goldberg does not disclose or even remotely suggest to one of ordinary skill in the art the repair of meniscal tissue by injecting into a joint a liquid suspension including an effective amount of mesenchymal stem cells, Goldberg does not anticipate Applicants' invention as claimed, nor does Goldberg render Applicants' invention as claimed obvious to one of ordinary skill in the art. It is therefore respectfully requested that the rejection under 35 U.S.C. 102 (b) be reversed.

For the above reasons and others, the claims on appeal are not anticipated by the cited references, and it is therefore respectfully requested that the rejections under 35 U.S.C. 102(e) and 35 U.S.C. 102(b) be reversed.

Respectfully submitted,

A handwritten signature in cursive script, appearing to read "Raymond J. Lillie".

Raymond J. Lillie

Registration No. 31,778

APPENDIX-CLAIMS ON APPEAL

28. A method of regenerating meniscal tissue in a joint of an animal, comprising:
injecting into said joint a liquid suspension consisting essentially of mesenchymal stem cells and an acceptable pharmaceutical carrier, whereby said mesenchymal stem cells differentiate into and/or stimulate production of meniscal tissue, and wherein said mesenchymal stem cells are injected in an amount effective to regenerate meniscal tissue in a joint of an animal.
29. The method of Claim 28 wherein said pharmaceutical carrier comprises hyaluronan or a salt thereof.
30. The method of Claim 29 wherein said hyaluronan or salt thereof is sodium hyaluronan.
31. The method of Claim 28 wherein said injection is into the joint space of said joint.
32. The method of Claim 28 wherein said joint is selected from the group consisting of knee joints, and the temporal mandibular joint.
33. The method of Claim 28 wherein said mesenchymal stem cells are autologous to the recipient.
34. The method of Claim 28 wherein said mesenchymal stem cells are allogeneic to the recipient.
35. A method of repairing meniscal damage in a joint, comprising:
injecting into said joint a liquid suspension consisting essentially of mesenchymal stem cells and an acceptable pharmaceutical carrier, whereby said mesenchymal stem cells differentiate into and/or stimulate production of meniscal tissue, said mesenchymal stem cells being injected in an amount effective to repair said meniscal damage in said joint.

36. The method of Claim 35 wherein said pharmaceutical carrier comprises hyaluronan or a salt thereof.
37. The method of Claim 36 wherein said hyaluronan or salt thereof is sodium hyaluronan.
38. The method of Claim 35 wherein said injection is into the joint space of said joint.
39. The method of Claim 35 wherein said joint is selected from the group consisting of knee joints, and the temporal mandibular joint.
40. The method of Claim 35 wherein said mesenchymal stem cells are autologous to the recipient.
41. The method of Claim 35 wherein said mesenchymal stem cells are allogeneic to the recipient.
42. A method of preventing or reducing subchondral bone sclerosis in a joint, comprising:
injecting into said joint a liquid suspension consisting essentially of mesenchymal stem cells and an acceptable pharmaceutical carrier, whereby said mesenchymal stem cells differentiate into and/or stimulate production of meniscal tissue and, wherein said mesenchymal stem cells are injected in an amount effective to prevent or reduce subchondral bone sclerosis in a joint.
43. The method of Claim 42 wherein said pharmaceutical carrier comprises hyaluronan or a salt thereof.
44. The method of Claim 43 wherein said hyaluronan or salt thereof is sodium hyaluronan.
45. The method of Claim 42 wherein said injection is into the joint space of said joint.
46. The method of Claim 42 wherein said joint is selected from the group consisting of knee joints, and the temporal mandibular joint.

47. The method of Claim 42 wherein said mesenchymal stem cells are autologous to the recipient.

48. The method of Claim 42 wherein said mesenchymal stem cells are allogeneic to the recipient.

49. A method of preventing or reducing the formation of osteophytes in a joint, comprising:
injecting into said joint a liquid suspension consisting essentially of mesenchymal stem cells and an acceptable pharmaceutical carrier, whereby said mesenchymal stem cells differentiate into and/or stimulate production of meniscal tissue, and wherein said mesenchymal stem cells are injected in an amount effective to prevent or reduce the formation of osteophytes in a joint.

50. The method of Claim 49 wherein said pharmaceutical carrier comprises hyaluronan or a salt thereof.

51. The method of Claim 50 wherein said hyaluronan or salt thereof is sodium hyaluronan.

52. The method of Claim 49 wherein said injection is into the joint space of said joint.

53. The method of Claim 49 wherein said joint is selected from the group consisting of knee joints, and the temporal mandibular joint.

54. The method of Claim 49 wherein said mesenchymal stem cells are autologous to the recipient.

55. The method of Claim 49 wherein said mesenchymal stem cells are allogeneic to the recipient.

56. A method of protecting cartilage in a joint of an animal, comprising:
injecting into said joint a liquid suspension consisting essentially of mesenchymal stem cells and an acceptable pharmaceutical carrier, whereby said mesenchymal stem cells

differentiate into and/or stimulate production of meniscal tissue adjacent said cartilage, and wherein said mesenchymal stem cells are injected in an amount effective to protect cartilage in a joint of an animal.

57. The method of Claim 56 wherein said pharmaceutical carrier comprises hyaluronan or a salt thereof.

58. The method of Claim 57 wherein said hyaluronan or salt thereof is sodium hyaluronan.

59. The method of Claim 56 wherein said injection is into the joint space of said joint.

60. The method of Claim 56 wherein said joint is selected from the group consisting of knee joints and the temporal mandibular joint.

61. The method of Claim 56 wherein said mesenchymal stem cells are autologous to the recipient.

62. The method of Claim 56 wherein said mesenchymal stem cells are allogeneic to the recipient.

63. The method of Claim 28 wherein said mesenchymal stem cells are present in said liquid suspension in an amount of from about 1×10^4 cells to about 1.5×10^8 cells.

64. The method of Claim 63 wherein said mesenchymal stem cells are present in said liquid suspension in an amount of from about 1×10^5 cells to about 1×10^8 cells.

65. The method of Claim 64 wherein said mesenchymal stem cells are present in said liquid suspension in an amount of from about 1×10^6 cells to about 1×10^7 cells.

66. The method of Claim 35 wherein said mesenchymal stem cells are present in said liquid suspension in an amount of from about 1×10^4 cells to about 1.5×10^8 cells.

67. The method of Claim 66 wherein said mesenchymal stem cells are present in said liquid suspension in an amount of from about 1×10^5 cells to about 1×10^8 cells.

68. The method of Claim 67 wherein said mesenchymal stem cells are present in said liquid suspension in an amount of from 1×10^6 cells to about 1×10^7 cells.
69. The method of Claim 42 wherein said mesenchymal stem cells are present in said liquid suspension in an amount of from about 1×10^4 cells to about 1.5×10^8 cells.
70. The method of Claim 69 wherein said mesenchymal stem cells are present in said liquid suspension in an amount of from about 1×10^5 cells to about 1×10^8 cells.
71. The method of Claim 70 wherein said mesenchymal stem cells are present in said liquid suspension in an amount of from about 1×10^6 cells to about 1×10^7 cells.
72. The method of Claim 49 wherein said mesenchymal stem cells are present in said liquid suspension in an amount of from about 1×10^4 cells to about 1.5×10^8 cells.
73. The method of Claim 72 wherein said mesenchymal stem cells are present in said liquid suspension in an amount of from about 1×10^5 cells to about 1×10^8 cells.
74. The method of Claim 73 wherein said mesenchymal stem cells are present in said liquid suspension in an amount of from about 1×10^6 cells to about 1×10^7 cells.
75. The method of Claim 56 wherein said mesenchymal stem cells are present in said liquid suspension in an amount of from about 1×10^4 cells to about 1.5×10^8 cells.
76. The method of Claim 75 wherein said mesenchymal stem cells are present in said liquid suspension in an amount of from about 1×10^5 cells to about 1×10^8 cells.
77. The method of Claim 76 wherein said mesenchymal stem cells are present in said liquid suspension in an amount of from about 1×10^6 cells to about 1×10^7 cells.

EVIDENCE APPENDIX

No evidence was submitted pursuant to 37CFR 1.130, 1.131, or 1.132.

RELATED PROCEEDINGS APPENDIX

There are no decisions rendered by a court or the Board in any related proceeding.

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